Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease of presumed autoimmune etiology that affects predominantly middle-aged women [1]. Contemporary epidemiologic studies indicate annual incidence rates for PBC ranging between 0.7 and 49 cases per million population and prevalence rates ranging between 6.7 and 402 cases per million population [2]. In the United States, national estimates for incidence and prevalence of PBC are approximately 3500 new cases each year with 47,000 prevalent cases among the white population [3]. Most patients are asymptomatic at the time of the diagnosis and identified as the result of the widespread use of serum liver biochemistries as part of routine screening.

Histologically, PBC is characterized by portal inflammation and necrosis of the epithelial cells in the small- and medium-sized bile ducts [4], which occur at different rates and with varying degrees of severity in different patients [5]. PBC is a slowly progressive disease that causes substantial loss of intrahepatic bile ducts, leading to interference with bile flow and hepatic accumulation of conjugates of hydrophobic bile acids, which perpetuate the cholestasis-associated liver damage, ultimately resulting in advanced fibrosis, cirrhosis, and liver failure. As such, PBC is an important indication for liver transplantation [1].

Historically, the median survival from time of diagnosis has been estimated at 10 years [6,7], although most of the studies from which these data are derived were performed at tertiary referral centers [2]. The most common cause of death in symptomatic patients who have PBC is still liver failure [8]. Once liver failure develops, liver transplantation is the only
effective treatment for eligible patients [9]. PBC once was the leading cause for liver transplantation, but effective therapy has reduced the need for transplantation in this group of patients and improved life expectancy [10].

Ursodeoxycholic acid (UDCA) has been the drug evaluated most widely in the treatment of PBC. Treatment with UDCA may delay disease progression and prolong survival free of liver transplantation [11–13], particularly in patients whose alkaline phosphatase levels are lower than twice the upper limit of normal after 6 months of therapy [14] and patients who have early-stage disease [15,16]. Currently, treatment with UDCA (in a dosage of 13 to 15 mg/kg per day) is recommended as therapy for PBC by the American Association for the Study of Liver Diseases [17] and approved for this indication by the United States Food and Drug Administration.

More than 20 years after the initial observation of favorable biochemical effects of UDCA in patients who have chronic active hepatitis [18] and the first pilot study on treatment of PBC with UDCA [19], several randomized, placebo-controlled clinical trials demonstrating beneficial effects of UDCA have been conducted. Currently, UDCA is widely accepted as the standard medical treatment for PBC; however, the evidence-based demonstration of its beneficial effect on survival remains controversial.

**Ursodeoxycholic acid**

UDCA, the 7-beta epimer of chenodeoxycholic, is a hydrophilic naturally occurring bile acid that seems to have fewer hepatotoxic properties than endogenous bile acids [10]. Although several trials have been conducted to evaluate the effects of UDCA in patients who have PBC, its mechanism of action is not fully known. UDCA has several interrelated functions, including expansion of the hydrophilic bile acid pool and as direct choleretic, anti-inflammatory and anti-apoptotic effects on hepatic epithelia [20,21]. In humans, naturally occurring UDCA accounts for up to 4% of the bile acid pool and likely originates in the colon by bacterial epimerization of the primary bile acid chenodeoxycholic [22]. After its formation, UDCA is absorbed by the ileal and colonic mucosa to enter the portal circulation and subsequently the pool of bile acids. After oral administration in clinical practice, UDCA may reduce the ileal absorption of endogenous bile acids by competitive inhibition at the level of the terminal ileum [20]. Eventually, with therapy, UDCA becomes the predominant bile acid, accounting for up to 40% or 50% of the total bile acid pool [21].

**Dosage**

In an early study with three different doses of UDCA in patients who had chronic liver disease, including PBC, Podda and colleagues [23] showed highly significant decreases in serum liver biochemistries, at dosages of
4 to 5 mg/kg per day, but the two higher dosages (8–10 mg/kg per day and 12–15 mg/kg per day) induced further improvements in serum enzyme levels, especially in patients who had PBC. Furthermore, the improvements were approximately proportional to the enrichment of conjugated biliary bile acids with UDCA [23]. More recently, a significant correlation has been found between the degree of bile enrichment and improvement in liver biochemistries and PBC Mayo risk score [7], suggesting that higher doses of UDCA might be associated with better results [24,25]. When three doses of UDCA (5–7 mg/kg, 13–15 mg/kg, and 23–25 mg/kg) were compared in 155 patients (low dose, standard dose, and high dose, respectively), improvement in biochemical profile, Mayo risk score, and UDCA enrichment were significantly greater in the standard-dose and high-dose groups compared to the low-dose group but not between the standard-dose and high-dose groups [26]. These data suggest that the optimal (safest and most cost-effective) dosage for UDCA is 13 to 15 mg/kg per day and are corroborated by findings of randomized clinical trials [13]. Whereas the daily recommended dose of UDCA in some studies initially was administered in multiple doses (three or four daily), administration of UDCA in one or two daily dose provides equivalent results on liver biochemistries and biliary enrichment with UDCA [25] and may improve patient compliance with the treatment regimen.

Effect on liver biochemistries

Early trials show that UDCA improves serum liver tests, including bilirubin and other markers of cholestasis [11,19,27–29]. Long-term follow-up studies show that improvement in liver biochemistries can be sustained; however, interruption of UDCA therapy is associated with deterioration in liver biochemistries, indicating the treatment is needed indefinitely [30].

Effect on symptoms

Six randomized controlled trials reported the effect of UDCA treatment on the symptoms of fatigue and pruritus [11,27–29,31,32]. None of the studies showed any significant effect on fatigue. Only one study reported a significant reduction of pruritus in the UDCA group compared with the placebo group [31]. There was no effect of UDCA on autoimmune conditions [33] or on bone disease in PBC [34].

Effect on portal hypertension

Therapy with UDCA seems to reduce the onset and severity of portal hypertension.

Neither portal pressure nor patients developing hepatic encephalopathy seems significantly affected by UDCA intervention. The number of patients developing ascites, however, is significantly lower in patients who receive
UDCA compared to patients receiving placebo in combined analyses [11,27,29,32].

Esophageal varices usually are regarded as a late complication of liver disease, but might happen earlier during the course of PBC. Furthermore, in contrast to patients who have other liver diseases, in whom bleeding from esophageal varices usually occurs later, patients who have PBC may have bleeding early in the course of the disease, before the onset of jaundice or true cirrhosis [5,35,36]. The reported effects of UDCA on the development of esophageal varices are conflicting. In one study, UDCA has been shown to delay the development of esophageal varices in early-stage PBC [37]. Two independent studies did not find any effect of UDCA on the development of esophageal varices [29,38], and many other studies did not address this issue.

**Effect on histology**

Although several studies show no histologic benefit to UDCA therapy for 2 to 4 years [11,28,39,40], other studies show that longer follow-up may be necessary to detect a clear histologic benefit [32,41–43]. One study evaluated the effect of UDCA treatment on histologic progression using a combined data set of individual histologic data of four larger placebo-controlled trials [11,27,28,32]. A total of 367 patients who had paired liver-biopsy specimens with a time interval of approximately 36 months between biopsies were studied [44]. Overall, there was no significant difference in the progression of the histologic stage when all patients were included. In a subgroup of patients who had initial stages I–II, comprising 177 patients, there was a significant decrease in the histologic stage progression in UDCA group relative to the placebo group. A trend to a lower progression rate was found in the noncirrhotic patients (stages I–III). These data suggest that initiating the drug when patients are at an earlier histologic stage is beneficial.

**Effect on survival**

Most of the trials of UDCA have not recruited sufficient patients to have the power to show an effect of therapy on survival [45]; therefore, the evidence that UDCA inhibits the progression of the disease has been delayed and fragmented since the completion of the trials that demonstrated improvement in markers of cholestasis [46].

Several studies evaluating long-term survival of patients who had biochemical response to UDCA are published. Most of those studies indicate that patients who have PBC treated with the recommended dosage of UDCA for a long period of time have longer survival free of transplantation and overall survival, particularly in the group of patients who have biochemical response to UDCA.

A small study by Leuschner and colleagues [47] of 22 patients who had PBC (14 of whom had early stages of disease) treated with UDCA
(at a dosage of 10 mg/kg per day for 4 to 12 years) showed a beneficial effect on symptoms and the progression of the disease in patients who had early disease. In one study of 180 patients who had PBC and were treated with UDCA for up to 6 years, Lindor and colleagues [12] reported that UDCA prolonged transplant-free survival. A recent study by Corpechot and colleagues [15] of 262 patients who received UDCA daily for a mean of 8 years, using a multistate Markov model, concluded that survival without liver transplantation was only slightly lower than the survival of an age- and gender-matched healthy control population and that treatment with UDCA could normalize the survival rate of patients who have PBC when given at early stages. In a study that included 192 patients treated with UDCA for a mean of 6.7 years, Pares and colleagues [48] reported that biochemical response to UDCA after 1 year is associated with a similar survival to the matched control population, supporting the favorable effects of this treatment in PBC. A study by Poupon and colleagues [49], which included 225 UDCA-treated patients, with 10-year follow-up showed survival benefit compared to the survival predicted by the well-validated Mayo risk model [7]. In this study, the difference between 10-year survival among UDCA-treated patients and that of an age- and gender-matched general population was explained mainly by mortality among cirrhotic patients. A recent study by ter Borg and colleagues [16], which included 297 patients treated with UDCA followed for a median period of 5.7 years, showed that survival without orthotopic liver transplantation in low-risk patients was significantly better than survival predicted by the Mayo risk model and that overall survival was only slightly lower than survival for an age- and gender-matched control group of the general population. Jackson and colleagues [50] found that patients who had PBC had a threefold mortality increase when compared with the general population, which was somewhat reduced by regular treatment with UDCA. This study included evaluation of the effects of UDCA in the development of primary liver cancer and showed that the increased risk for primary liver cancer in UDCA treated patients was threefold, in contrast to an eightfold increase in those not treated.

In contrast, other studies have not shown beneficial effects of UDCA. In a trial with 86 patients randomly assigned to UDCA or placebo, who were observed up to 12 years (mean 7.3 years), UDCA was not found to improve survival [51]. In this study, however, more than one third of the patients assigned to placebo were crossed over to UDCA at their request after variable time intervals, mostly because of clinical deterioration. Similarly, negative findings were noted when 151 patients randomly assigned to UDCA (10–12 mg/kg daily) or placebo (for 2 years and then patients were offered open-label extension) were observed for up to 6 years [52]. In a community-based study in England, UDCA did not improve survival in the 261 patients who received the medication [8]. In an independent study conducted in England, which included 209 patients, 69 of whom received UDCA for a mean of 5.8 years, UDCA did not seem to alter disease progression in
patients despite a significant improvement in liver biochemistries [38]. The United Kingdom experience seems to some extent different from that of other European countries, in that they tend to use a lower dosage (6–8 mg/kg daily) and start therapy later in the course of the disease [53].

Analysis of the combined data from three large, well-designed, controlled trials that used adequate UDCA doses up to 4 years, including a total of 548 patients, showed that UDCA significantly reduced the likelihood of liver transplantation or death [13]. This significant effect was seen despite the fact that in two of the individual studies, patients randomized to placebo were offered open-label treatment with UDCA after 2 years, which makes the beneficial effects of UDCA harder to detect.

These positive results of UDCA on survival and survival free of liver transplantation have been challenged by two meta-analyses [54,55] and a Cochrane review [56]. The meta-analyses have several limitations. Most published randomized controlled trials have shown beneficial effects of UDCA on biochemical parameters. None of these trials, however, were of sufficient power to be able to find a significant decrease in the incidence rates of death or liver transplantation. PBC is a slowly progressive disease, and the small sample size and short duration of several trials included in these meta-analyses explain at least in part their inability to detect significant effects of UDCA on survival or survival without liver transplantation [53]. Furthermore, many trials included in these combined analysis administered low dosages of UDCA (<10 mg/kg daily), which are known to be suboptimal [26]. Other issues that make trials more complex to evaluate is the wide range of disease severity together with the fact that the magnitude of UDCA action seems inversely correlated to the disease stage [53] and the fact that not all of the patients have complete response to UDCA [24].

In contrast, three independent meta-analyses have shown positive results of UDCA on survival in patients who had PBC [57–59]. An early meta-analysis including randomized controlled trials and clinical series of the use of UDCA in PBC concluded that UDCA had a beneficial effect in PBC on liver biochemistries, liver histology, and treatment failure (described as doubling of bilirubin, consideration of liver transplantation, and liver-related death) [57]. A major limitation of this study is the inclusion of clinical series. One meta-analysis was published in correspondence form, showing that long-term treatment with the optimal dose of UDCA could improve survival free of liver transplantation [58]. One recent meta-analysis that included only randomized controlled trials where adequate dosages of UDCA (10–20 mg/kg per day) were administered and there was adequate follow-up time (>24 months) and subsequent reports of their extended follow-up concluded there was a significant reduction of the incidence of liver transplantation and a marginally significant reduction of the rate of death or liver transplantation, but not death alone, in the group of patients who received UDCA [59]. Furthermore, in the sensitivity analyses, which included studies administering placebo as control, long-term studies
(> 48 months), and large-sized studies (> 100 patients), long-term treatment with UDCA significantly reduced the incidence of liver transplantation and death or liver transplantation [59].

Finally, additional indirect support for a long-term beneficial effect of UDCA in PBC might come from retrospective studies of transplantation trends among patients who had PBC [53]. Several studies evaluating large series of patients in Europe and in the United States indicate that the proportion and the absolute number of patients transplanted for PBC are decreasing [53,60,61], whereas the incidence of the disease seems stable [3] and the prevalence rising [2].

Cost-effectiveness

Pasha and colleagues [62] evaluated the cost-effectiveness of UDCA therapy in PBC based on data from two previously published trials [11,28]. The effectiveness of UDCA was determined by comparing the annual reduction in the development of ascites, esophageal varices, variceal bleeding, encephalopathy, liver transplantation, and death between the treatment groups. They concluded that patients receiving UDCA had a lower incidence of major complications (mainly esophageal varices and liver transplantation) and lower medical care costs compared to patients receiving placebo [62].

Side effects

UDCA seems safe and has few side effects. Some patients have weight gain, hair loss, and, rarely, diarrhea and flatulence [10]. UDCA is well tolerated and intolerance seldom leads discontinuation from clinical trials, even when higher doses (23 to 25 mg/kg) were administered daily [26].

Suboptimal response to ursodeoxycholic acid

In at least 25% to 30% of patients who have PBC who are treated with UDCA, a complete response occurs, characterized by normal biochemical test results and stabilized or improved histologic findings in the liver [24,63]. Unfortunately, some patients have an incomplete response to the standard treatment for these diseases and have a progressive disease that eventually leads to liver transplantation or death from liver-related causes. Various unknown factors could be associated with nonresponse to therapy, but these are not elucidated to date. Serum alkaline phosphatase levels at 6 months can be helpful in predicting response to UDCA [14,48]. The suboptimal response to UDCA and the increased risk for nonresponders of progressing to clinical failure endpoints has elicited interest with regards for further treatment. Various combinations of agents with UDCA also have been studied. (Some of these studies are discussed later.) An increment in the dose of UDCA in patients who had incomplete response to UDCA was not found of any benefit in this subpopulation of patients [64].
Other choleretic agents

The pathophysiologic findings of interference with bile flow and hepatic accumulation of conjugates of hydrophobic bile acids, which perpetuate the cholestasis-associated liver damage and positive effects of UDCA in PBC, have led to the search for potent, long-acting choleretic agents that can be beneficial in the treatment of cholestatic liver disease.

**Rifampin (rifampicin)**

Rifampin is known to interfere with the hepatic elimination of endogenous compounds and xenobiotics in physiologic and pathologic conditions [65]. In normal subjects, rifampin enhances bile acid detoxification and bilirubin conjugation and excretion, and the combination of rifampin and UDCA has synergistic effects on hepatobiliary transport and detoxification systems [66]. In small studies with patients who have chronic cholestatic diseases, rifampin improves pruritus [67–70] and decreases serum concentrations of bile acids [67,71], alkaline phosphatase [67,71], aminotransferases [71], and bilirubin [67]. The precise mechanisms by which rifampin acts in cholestasis remain unclear but may include a selective interaction of rifampin with the hepatobiliary transport of bilirubin [65]. Currently, because of the risk for drug-induced hepatitis, reported to occur in approximately 7% to 13% of patients during long-term treatment [71,72], the use of rifampin is limited to the treatment of pruritus not responding to bile acid sequestrates. Further investigation of combination therapy of rifampin and UDCA might prove beneficial in patients who have PBC.

**Sulindac**

Sulindac is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties found to have additional choleretic properties in rats [73]. These properties have led to its evaluation as an adjuvant agent for treatment in patients who have PBC. A small open-label study to investigate the combination of sulindac with UDCA was conducted over a period of 12 months [74]. Twenty-three patients who had incomplete response to UDCA were randomized to UDCA and sulindac combination and UDCA alone. Sulindac was associated with further improvement in liver biochemistries and was well tolerated. Further studies need to be performed to confirm these beneficial effects.

**Norursodeoxycholic acid**

Norursodeoxycholic acid (norUDCA) is the C23 (C24-nor) homolog of UDCA. In animal studies, administration of norUDCA seems to restore bile alkalinity and bile flow in knockout mice lacking the cystic fibrosis
gene product, in which deficient bicarbonate secretion by cholangiocytes occurs [75]. In the mdr2 knockout mouse, whose phenotype is absent biliary phospholipid secretion, norUDCA but not UDCA markedly improved liver biochemistry and histology and significantly reduced hydroxyproline content and the number of infiltrating neutrophils and proliferating hepatocytes and cholangiocytes [76]. In healthy human volunteers, norUDCA ingestion induces hypercholeresis and evokes less phospholipid and cholesterol secretion into bile than UDCA. Translational studies in humans are required.

Immunosuppressive agents

Despite the presumed autoimmune etiology of PBC, a clear benefit from immunosuppressive agents has not been demonstrated to date [77–79] and their use is limited by side effects.

A variety of immunosuppressive medications have been used alone or with UDCA in patients who have PBC, in particular those who have incomplete response to UDCA monotherapy. Medications evaluated include azathioprine, budesonide, chlorambucil, cyclosporine, methotrexate, mycophenolate mofetil (MMF), prednisone, prednisolone, rituximab, and tacrolimus. Some small studies suggest that combination therapy may be superior to UDCA monotherapy [80–82] but further studies are necessary. At present, there are insufficient data to support the use of immunosuppressive therapy for PBC [83].

Azathioprine

The first clinical trial of azathioprine in PBC involved 45 patients randomized to 2 mg/kg per day or no medication, and no treatment effect was observed [84]. A larger study, with 232 patients, randomized to 1 mg/kg per day of azathioprine, initially reported no benefit in survival, clinical course, hepatic histologic features, hepatic tests, or immunologic abnormalities after a median follow-up period of 18 months [85]. After extended follow-up, the same group reported that azathioprine treatment in 248 patients was associated with a small but statistically significant benefit, improving survival by an average of 20 months [86]. This was demonstrated only after a series of complex statistical corrections, and many patients were lost to follow-up or had incomplete data and subsequently were excluded for the analysis [45]. These studies demonstrate that azathioprine monotherapy has no value in the treatment of PBC [84–86]. In one trial, however, azathioprine in combination with prednisone and UDCA had a beneficial effect on liver biochemistries, serum markers of fibrosis, and liver histology [80]. Azathioprine may have a role in reducing the dose of corticosteroids, hence limiting side effects associated with those agents.
Clorambucil

One small, randomized pilot study with 24 patients was conducted to evaluate the use of chlorambucil in patients who have PBC [87]. Even though there was a modest effect on serum aminotransferase, bilirubin, and albumin in the treatment group (13 patients), suggesting that chlorambucil therapy may retard the progression of the disease, side effects of therapy included bone marrow suppression necessitating discontinuation of the drug in four patients [87].

Corticosteroids

The combination of UDCA and corticosteroids, such as prednisolone or budesonide, may lead to improvement in alkaline phosphatase activity and aminotransferases and histologic damage, at least in the short term. Unfortunately, the development of side effects with these corticosteroids, particularly in bone mass, greatly precludes the use of corticosteroids in patients who have PBC, especially those who have advanced disease who are at greater risk for osteoporosis [77,79]. Alendronate has been studied and found to improve bone mineral density in patients who have PBC [88], as have other bisphosphonates or raloxifene [89], and could be useful in reducing that potential risk.

Prednisone

In a retrospective study, Wolfhagen and colleagues [90] reported beneficial effects on symptoms and biochemical parameters when seven symptomatic patients who had early-stage PBC and incomplete response to UDCA received prednisone in addition to UDCA. In a subsequent study (described previously), the combination of prednisone, UDCA, and the steroid-sparing azathioprine had a beneficial effect on liver biochemistries, serum markers of fibrosis, and liver histology [80].

Prednisolone

Initial results of treatment with prednisolone in a controlled fashion in patients who had PBC were disappointing: minimal improvement in biochemical or histologic measurements was observed [77]. Leuschner and colleagues [91] conducted a short-term study in 30 patients who had mostly early PBC and were randomized to combination therapy of UDCA (at a dosage of 11 to 13 mg/kg daily) and prednisolone (10 mg daily) or UDCA alone for 9 months. Combination therapy was not superior to monotherapy with UDCA with regard to liver function tests, but it had a highly beneficial influence on liver histology [91]. Despite low-dose administration for a short period of time, side effects were observed in the group of patients receiving steroids: two patients had Cushing’s syndrome, two patients had hirsutism, and bone densitometry revealed a slight deterioration.
of pre-existing osteoporosis in one patient, a significant limitation to long-term use of prednisolone combination therapy in clinical practice.

**Budesonide**

Budesonide is a newer steroid structurally related to 16-α-hydroxyprednisolone that has an extensive first-pass hepatic metabolism and reported minimal systemic availability [92]. Because of its 15- to 20-times higher glucocorticoid receptor-binding affinity, the effect of budesonide on liver inflammatory activity may be greater than that of prednisolone [93]. Oral budesonide is shown to exert fewer side effects than conventional corticosteroids in patients who have inflammatory bowel disease [94] and, therefore, seems an attractive drug for use in PBC.

Budesonide has been studied in patients who have PBC responding sub-optimally to UDCA in the authors’ institution and showed no benefit for those patients but had the potential for significant worsening of the underlying osteopenic bone disease [79]. Twenty-two patients who had PBC regardless of the stage of disease received budesonide (3 mg 3 times daily for 1 year). Despite transient improvement in liver biochemistries, including bilirubin, the Mayo risk score increased significantly and budesonide was associated with a significant worsening of osteoporosis in patients who had PBC [79].

In contrast, previous small studies with budesonide have been performed in nonselected patients who had early stages of PBC and had shown positive effects of combination therapy on liver histology and laboratory values with short-term therapy. Leuschner and colleagues [81] conducted a randomized, controlled, double-blinded trial over 2 years in which 20 patients who had early-stage PBC using UDCA (at a dosage of 10 to 15 mg/kg per day) with oral budesonide (3 mg 3 times daily) were compared with 19 patients receiving UDCA plus placebo. This study showed that combination therapy is superior to monotherapy with UDCA but detrimental changes in bone mineral density after 2 years were more pronounced [81]. Another randomized, multicenter study by Rautiainen and colleagues [82] included 77 patients who had noncirrhotic stages of PBC (stages I–III). Forty-one patients received budesonide (6 mg daily) in addition to UDCA (15 mg/kg per day) and 36 patients received UDCA alone for a total of 3 years, and the combination of UDCA and budesonide was associated with significantly improved liver histology [82]. Side effects of corticosteroids led to discontinuation of budesonide in only one patient, and seven other patients reported mild glucocorticoid-related effects, suggesting that further studies of budesonide administration in patients who have early stages of PBC are warranted.

Recent data show that the metabolism of budesonide is strongly reduced in patients who have BC and who have histologic stage IV as compared to those who have stage I-II. In a pharmacokinetic trial, two of seven patients who had PBC in stage IV developed portal vein thrombosis probably related
to budesonide; one patient died [93]. These data suggest that budesonide should not be used in patients who have PBC and cirrhotic-stage disease or signs of portal hypertension.

Cyclosporine

Studies with cyclosporine in PBC are limited mostly by adverse effects on renal function. One small pilot study demonstrated beneficial effects on alkaline phosphatase but not on bilirubin in 40% of the 15 patients who received cyclosporine [95]. A larger study of 29 patients demonstrated beneficial effect on total serum bilirubin and liver histology; however, one third of the patients receiving cyclosporine discontinued therapy because of side effects and approximately two thirds of the patients on the drug had an elevation in their serum creatinine [96]. A large, randomized, double-blind, multicenter study with 349 patients demonstrated a beneficial effect on survival but was limited by adverse effects on renal function and systemic blood pressure [97]. The very high rate of side effects and difficulties of managing maintenance therapy with cyclosporine deter its use in patients who have PBC [45].

Methotrexate

Methotrexate has been evaluated extensively in patients who have PBC and data are conflicting.

Initial small studies with methotrexate showed encouraging results, resulting in improvement in liver biochemistries, symptoms, and liver histology [98]. Buscher and colleagues [99] treated eight consecutive patients who had incomplete response to UDCA with the addition of methotrexate (2.5 mg daily) to their regimen, with adequate biochemical response in seven of them and improvement of symptoms in all symptomatic patients. Babatin and colleagues [100] treated eight consecutive symptomatic patients who had an incomplete response to UDCA with methotrexate (at a dosage of 7.5 mg–15 mg weekly for a mean of 49 months). No significant adverse effects were documented, and there was improvement in symptoms in all patients (fatigue in 6/7 and pruritus in 6/7) and improvement in biochemical markers of cholestasis [100].

Other studies, however, did not demonstrate beneficial effects from methotrexate. Lindor and colleagues [101] treated 32 patients who had UDCA and placebo or UDCA and methotrexate. No obvious benefit was observed, and four patients withdrew from the study because of severe effects believed related to methotrexate [101]. Gonzalez-Koch and colleagues [102] treated 13 patients with low dosages of UDCA (500 mg per day) and methotrexate (10 mg per week) and 12 patients exclusively with UDCA. No significant toxicity was described, but no beneficial effects were reported [102]. Bach and colleagues [103] reported results from a multicenter study, including 110 patients who had PBC who received methotrexate (15 mg per week); for most patients, ursodeoxycholic acid was added during the study.
Methotrexate was not well tolerated, and only half of the study group completed 5 years of methotrexate therapy. Therapy with methotrexate did not prevent progression of disease, as indicated by a rising Mayo risk score, and did not diminish the risk for death or liver transplantation when compared with UDCA or placebo [103].

Results from larger studies are disappointing. Hendrickse and colleagues [104] conducted a single-center randomized controlled trial with 60 patients to evaluate the effect of methotrexate (7.5 mg per week for up to 6 years). They describe improvement in liver biochemistries and a trend toward improvement of pruritus; however, they also noted increases in serum bilirubin, Mayo risk score, and increased rate for death or liver transplantation as a result of liver disease during or after the trial, suggesting that low-dose methotrexate is not appropriate for the treatment of PBC [104]. A large multicenter trial including 265 patients evaluated the use of methotrexate (at weekly doses of 15 mg/m² body surface area) in combination with adequate doses of UDCA for a median period of 7.6 years [105]. There were no significant differences in parameters of treatment failure or to the time of development of treatment failures observed for patients taking UDCA plus methotrexate or UDCA plus placebo. The investigators conclude that methotrexate when added to UDCA had no effect on the course of PBC treated with UDCA alone [105].

In most studies, methotrexate (used in a dosage of 15–20 mg per week) was associated with toxicity. Side effects included fatigue, mouth ulcers, alopecia, marrow depression, and interstitial pneumonitis and led to reduction or withdrawal of the drug in approximately 15% of patients [99,101,106,107].

**Mycophenolate mofetil**

Mycophenolic acid is a noncompetitive, reversible inhibitor of inosine monophosphate dehydrogenase, the rate-limiting enzyme for de novo purine synthesis, disrupting proliferation of T and B cells [108]. The efficacy of mycophenolate mofetil (MMF) in treating azathioprine-refractory type 1 autoimmune hepatitis [109] has led to consideration of this agent in conditions, such as PBC. After encouraging results described in only two patients who had PBC who received MMF [110], a small trial of MMF (1–3 g per day) and UDCA combination therapy was conducted in 25 patients who had incomplete response to UDCA [111]. The addition of MMF to UDCA was not associated with important clinical benefits in PBC. Furthermore, six patients did not complete therapy; adverse drug events were responsible for study withdrawal in three individuals and adverse reactions that resolved spontaneously or by dose reduction occurred in 13 patients [111].

**Rituximab**

Rituximab is a chimeric mouse antihuman CD20 monoclonal antibody that ablates CD20-positive B cells and eliminates their antibody production
that has been used successfully to treat lymphomas, lymphoproliferative disorders, and a variety of immunoglobulin-mediated autoimmune disorders [108]. Preliminary data on rituximab, administrated in the form of two infusions at days 1 and 15 in 14 patients who had PBC and incomplete response to UDCA, show promise as a therapy for PBC [112], but more data are needed to confirm its safety and efficacy.

Summary

PBC is a presumed immune-mediated liver disease of middle-aged women associated with significant morbidity and mortality. UDCA is safe long term and seems of most benefit when instituted early in the course of the disease. Patients who have suspected PBC undergo evaluation to establish the diagnosis early and UDCA therapy should be initiated promptly as treatment with UDCA may delay disease progression and prolong survival free of liver transplantation. Patients who have late histologic stage and more abnormal liver biochemistries have a poorer prognosis despite UDCA therapy. Patients who have advanced disease or persistently abnormal liver tests even after UDCA therapy is introduced should be considered for therapeutic trials with other adjunctive agents. Despite the presumed autoimmune etiology of PBC, a clear benefit from immunosuppressive agents has not been demonstrated to date and their use can be limited by side effects. Further studies are needed for development of an optimal therapeutic strategy for patients who have PBC to cure or halt progression of disease, thereby decreasing incidence of complications of advanced liver disease and the need for transplantation and extending life expectancy in all patients who have PBC.

References


